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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Imidazopyridines

(72) Mederski, Werner - Germany (Federal Republic of) ;
Dorsch, Dieter - Germany (Federal Republic of) ;
Beier, Norbert - Germany (Federal Republic of) ;
Schelling, Pierre - Germany (Federal Republic of) ;
Lues, Ingeborg - Germany (Federal Republic of) ;
Minck, Klaus-Otto - Germany (Federal Republic of) ;

(71) Merck Patent Gesellschaft mit beschraenkter Haftung - Germany (Federal Republic of) ;

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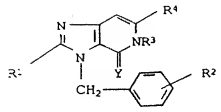
(57) 8 Claims

Abstract

Imidazopyridine derivatives of formula I:



I

wherein
R^1 to R^4 and Y have the meaning stated in Claim 1,
and their salts, exhibit antagonistic properties towards angiotensin II and have inter alia a hypotensive action.

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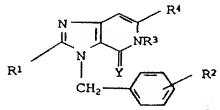
6100 D a r m s t a d t

Patent Claims

1. An imidazopyridine derivative of formula I:



I

wherein

R^1 is H or A,

R^2 is H, Hal, OH, OA, COOH, COOA, $CONH_2$, CN, NO_2, NH_2, NHA, $N(A)_2$, $NHCOR^5$, $NHSO_2R^5$ or 1H-5-tetrazolyl,

R^3 is H, cyanoalkyl, Ar-alkyl, cycloalkylalkyl having 3-8 C atoms in the cycloalkyl group, Het-alkyl, Ar'-alkyl, R^6-CO-alkyl, Ar-CO-alkyl or Het-CO-alkyl having, in each case, 1-6 C atoms in the 'alkyl' moiety, it being possible for an H atom in the 'alkyl' moiety to be replaced by a COOH or a COOA group,

R^4 is H or Hal,

R^5 and R^6 are in each case alkyl having 1-6 C atoms, wherein one or more H atom(s) can also be replaced by F,

Y is O or S,

A is alkyl, alkenyl or alkynyl in each case having up to 6 C atoms,

Ar is a phenyl group which is unsubstituted or monosubstituted by Hal, R^5, OH, OA, COOH, COOA, CN, NO_2, NH_2, NHA, $N(A)_2$, $NHCOR^5$, $NHSO_2R^5$ or 1H-5-tetrazolyl,

Ar' is a phenyl group substituted by Ar,

Het is a five or six-membered heteroaromatic radical having 1 to 3 N, O and/or S atoms, which can also be condensed with a benzene or pyridine ring, and

Hal is F, Cl, Br or I,

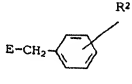
and their salts.

2. a) 2-Butyl-5-benzyl-3-p-carboxybenzyl-4,5-dihydro-4-oxo-3H-imidazo[4,5-c]pyridine and its salts;

b) 2-Butyl-3-p-carboxybenzyl-5-(2-thienylmethyl)-4,5-dihydro-4-oxo-3H-imidazo[4,5-c]pyridine and its salts;

c) 5-p-Aminobenzyl-2-butyl-3-p-carboxybenzyl-4,5-dihydro-4-oxo-3H-imidazo[4,5-c]pyridine and its salts.

3. Process for the preparation of imidazopyridines of formula I according to Claim 1, and their salts, characterised in that a compound of formula II



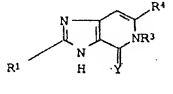
II

wherein

E is Cl, Br, I, a free OH group or an OH group which has been functionally modified to acquire reactivity, and

R^2 has the meaning stated in Claim 1,

is reacted with a compound of formula III



III

wherein
R^1, R^3, R^4 and Y have the meanings stated in Claim 1,
or in that a compound of formula I is liberated from one of its functional derivatives by treatment with a solvolysing or hydrogenolysing agent,
and/or in that one or more radical(s) R^1, R^2, R^3, R^4 and/or Y in a compound of formula I are converted to one or more other radicals R^1, R^2, R^3, R^4 and/or Y, and/or a base or acid of formula I is converted to one of its salts.

4. Process for the preparation of pharmaceutical formulations, characterised in that a compound of formula I according to Claim 1, and/or one of its physiologically acceptable acid addition salts, are incorporated into a suitable dosage form together with at least one solid, liquid or semi-liquid excipient or adjunct.

5. Pharmaceutical formulation, characterised in that it contains at least one compound of formula I according to Claim 1, and/or one of its physiologically acceptable acid addition salts.

6. Compound of formula I according to Claim 1, and its physiologically acceptable acid addition salts, for the control of diseases.

7. Use of compounds of formula I according to Claim 1, and/or their physiologically acceptable acid addition salts, for the preparation of a drug.

8. Use of compounds of formula I according to Claim 1, and/or their physiologically acceptable acid addition salts, in the control of diseases.

Fetherstonhaugh & Co.,
Ottawa, Canada
Patent Agents

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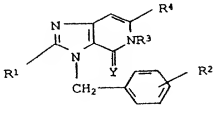
6100 D a r m s t a d t

Imidazopyridines

The invention relates to novel imidazopyridine derivatives of formula I:



I

wherein

R^1 is H or A,

R^2 is H, Hal, OH, OA, COOH, COOA, $CONH_2$, CN, NO_2, NH_2, NHA, $N(A)_2$, $NHCOR^5$, $NHSO_2R^5$ or 1H-5-tetrazolyl,

R^3 is H, cyanoalkyl, Ar-alkyl, cycloalkylalkyl having 3-8 C atoms in the cycloalkyl group, Het-alkyl, Ar'-alkyl, R^6-CO-alkyl, Ar-CO-alkyl or Het-CO-alkyl having, in each case, 1-6 C atoms in the 'alkyl' moiety, it being possible for an H atom in the 'alkyl' moiety to be replaced by a COOH or a COOA group,

R^4 is H or Hal,

R^5 and R^6 are in each case alkyl having 1-6 C atoms, wherein one or more H atom(s) can also be replaced by F,

Y is O or S,

A is alkyl, alkenyl or alkynyl in each case having up to 6 C atoms,

Ar is a phenyl group which is unsubstituted or monosubstituted by Hal, R^5, OH, OA, COOH, COOA, CN, NO_2, NH_2, NHA, $N(A)_2$, $NHCOR^5$, $NHSO_2R^5$ or 1H-5-

tetrazolyl,

Ar' is a phenyl group substituted by Ar,

Het is a five or six-membered heteroaromatic radical having 1 to 3 N , O and/or S atoms, which can also be condensed with a benzene or pyridine ring, and

Hal is F, Cl, Br or I,

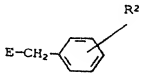
and their salts.

The object of the invention was to find novel compounds with valuable properties, especially compounds which can be used for the preparation of drugs.

It has been found that the compounds of formula I and their salts possess very valuable pharmacological properties coupled with a good tolerance. In particular, they exhibit antagonistic properties towards angiotensin II and can therefore be used as pharmaceutical active ingredients in human and veterinary medicine, especially for the prophylaxis and/or therapy of cardiac, circulatory and vascular diseases and in particular for the treatment of angiotensin II-dependent hypertension, aldosteronism and cardiac insufficiency, as well as disorders of the central nervous system, furthermore of hypertrophy and hyperplasy of the blood vessels and the heart, angina pectoris, cardiac infarction, haemorrhagic stroke, restenosis after angioplasty or by-pass surgery, arteriosclerosis, ocular hypertension, glaucoma, macular degeneration, hyperuricaemia, disturbances of the renal functions such as renal failure, diabetic complications such as nephropathia diabetica or retinopathia diabetica, psoriasis, angiotensinII-induces disturbances in female sexual organs, cognitive disorders, f.e. dementia, amnesia, disturbances of the functions of memory, states of fear, depressions and/or epilepsy.

These effects can be determined by conventional in vitro or in vivo methods such as those described for example in US Patent 4 880 804 and in WO 91/14367, as well as those described by A.T. Chiu et al., J. Pharmacol. Exp. Therap. 250, 867-874 (1989), and by P.C. Wong et al., ibid. 252, 719-725 (1990; in vivo, on rats).

The invention relates to the compounds of formula I, their salts and to a process for the preparation of these compounds and their salts, characterised in that a compound of formula II:



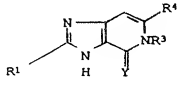
II

wherein

E is Cl, Br, I, a free OH group or an OH group which has been functionally modified to acquire reactivity, and

R^2 has the meaning stated in Claim 1,

is reacted with a compound of formula III



III

wherein

R^1, R^3, R^4 and Y have the meanings stated in Claim 1,

or in that a compound of formula I is liberated from one of its functional derivatives by treatment with a solvolysing or hydrogenolysing agent,

and/or in that one or more radical(s) R^1, R^2, R^3, R^4 and/or Y in a compound of formula I are converted to one or more other radicals R^1, R^2, R^3, R^4 and/or Y, and/or a base or acid of formula I is converted to one of its salts.

Hereinabove and hereinafter, the radicals or parameters R^1 to R^8, Y, A, Ar, Ar', Het, Hal and E have the meanings stated in formulae I and II, unless expressly indicated otherwise.

In the above formulae, A is particularly alkyl having 1-6, preferably 1, 2, 3 or 4 C atoms, preferably methyl, or else ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, or else pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl or 1,1,2- or 1,2,2-trimethylpropyl. However, A can also be alkenyl or alkynyl in each case having 2-6, preferably 2, 3 or 4 C atoms, in particular vinyl, 1- or 2-propenyl (allyl), 1-propen-2-yl, 1-, 2- or 3-butenyl,

ethynyl, 1- or 2-propynyl (propargyl), 1-, 2- or 3-butynyl.

Accordingly, the radical OA is preferably methoxy, or else ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, vinyloxy, allyloxy, ethynyloxy or propargyloxy. The group COOA is preferably methoxycarbonyl or ethoxycarbonyl, or else propyloxycarbonyl, isopropyloxycarbonyl, butyloxycarbonyl, isobutyloxycarbonyl, allyloxycarbonyl, propargyloxycarbonyl. The group NHA is preferably methylamino or ethylamino. The group $N(A)_2$ is preferably dimethylamino or diethylamino.

Hal is preferably F, Cl or Br, or else I.

The radical Ar is preferably an unsubstituted phenyl group, or else preferably a phenyl group substituted in the p-position or substituted in the o- or m-position. Preferred substituents are COOH, COOA, NO_2 1H-5-tetrazolyl. Accordingly, Ar is preferably phenyl, o-, m- or (especially) p-carboxyphenyl, o, m- or (especially) p-methoxycarbonylphenyl, o-, m- or (especially) p-ethoxycarbonylphenyl, o-, m- or (especially) p-nitrophenyl, o-, m- or (especially) p-(1H-5-tetrazolyl)-phenyl furthermore preferably, o-, m- or (especially) p-aminophenyl, o-, m- or (especially) p-dimethylamino-phenyl, o-, m- or (especially) p-diethylaminophenyl, o-, m- or p-tolyl, o-, m- or p-trifluoromethylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-methoxyphenyl, o-, m- or p-fluorophenyl, o-, m- or p-chlorophenyl, o-, m- or p-bromophenyl, o-, m- or p-iodophenyl, o-, m- or p-cyanophenyl, o-, m- or p-methylaminophenyl, o-, m- or p-acetamidophenyl, o-, m- or p-trifluoroacetamidophenyl, o-, m- or p-methylsulfonamidophenyl, o-, m- or p-trifluoromethylsulfonamidophenyl.

The radical Ar' is preferably 4-biphenylyl, 2'-carboxy-4-biphenylyl, 2'-methoxycarbonyl-4-biphenylyl, 2'-cyano-4-biphenylyl or 2'-(1H-5-tetrazolyl)-4-biphenylyl.

Het is preferably 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 2,1,5-thiadiazol-3- or -4-yl, 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1H-1-, -2-, -5-, -6- or -7-imidazo[4,5-b]pyridyl, 3H-2-, -3-, -5-, -6- or -7-imidazo[4,5-b]pyridyl, 1H-1-, -2-, -4-, -6- or -7-imidazo[4,5-c]pyridyl, 3H-2-, -3-, -4-, -6- or -7-imidazo[4,5-c]pyridyl.

The term "Het" also includes the homologous radicals in which the heteroaromatic ring is substituted by one or more, preferably 1 or 2, A groups, preferably methyl and/or ethyl groups, for example 3-, 4- or 5-methyl-2-furyl, 2-, 4- or 5-methyl-3-furyl, 2,4-dimethyl-3-furyl, 3-, 4- or 5-methyl-2-thienyl, 3-methyl-5-tert.-butyl-2-thienyl, 2-, 4- or 5-methyl-3-thienyl, 2- or 3-methyl-1-pyrrolyl, 1-, 3-, 4- or 5-methyl-2-pyrrolyl, 3,5-dimethyl-4-ethyl-2-pyrrolyl, 2-, 4- or 5-methyl-1-imidazolyl, 4-methyl-5-pyrazolyl, 4- or 5-methyl-3-isoxazolyl, 3- or 5-methyl-4-isoxazolyl, 3- or 4-methyl-5-isoxazolyl, 3,4-dimethyl-5-isoxazolyl, 4-,or 5-methyl-2-thiazolyl, 4- or 5-ethyl-2-thiazolyl, 2- or

5-methyl-4-thiazolyl, 2- or 4-methyl-5-thiazolyl, 2,4-dimethyl-5-thiazolyl, 3-, 4-, 5- or 6-methyl-2-pyridyl, 2-, 4-, 5- or 6-methyl-3-pyridyl, 2- or 3-methyl-4-pyridyl, 4-methyl-2-pyrimidinyl, 4,6-dimethyl-2-pyrimidinyl, 2-, 5- or 6-methyl-4-pyrimidinyl, 2,6-dimethyl-4-pyrimidinyl, 3-, 4-, 5-, 6- or 7-methyl-2-benzofuryl, 2-ethyl-3-benzofuryl, 3-, 4-, 5-, 6- or 7-methyl-2-benzothienyl, 3-ethyl-2-benzothienyl, 1-, 2-, 4-, 5-, 6- or 7-methyl-3-indolyl, 1-methyl-5- or 6-benzimidazolyl, 1-ethyl-5- or 6-benzimidazolyl.

The radical Y is preferably O.

The radical R^1 is preferably A, in particular butyl, furthermore preferably propyl, pentyl or hexyl.

The radical R^2 is preferably COOH, furthermore preferably 1H-5-tetrazolyl, $COOCH_3$, $COOC_2H_5$, $CONH_2$, CN or NO_2.

The "alkyl" moiety in the radical R^3 is in the individual groups preferably $-CH_2-$ or $-CH_2CH_2-$, furthermore preferably $-CH(CH_3)-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$ or $-(CH_2)_6-$. Specifically, R^3 is preferably H; Ar-alkyl such as benzyl, 1- or 2-phenylethyl, o-, m- or (especially) p-carboxybenzyl, o-, m- or (especially) p-methoxycarbonylbenzyl, o-, m- or (especially) p-ethoxycarbonylbenzyl, o-, m- or (especially) p-nitrobenzyl, o-, m- or (especially) p-aminobenzyl, o-, m- or (especially) p-cyanobenzyl; cycloalkylalkyl such as cyclopropylmethyl, cyclobutyl-methyl, cyclopentylmethyl, cyclohexylmethyl, 1- or 2-cyclohexylethyl, cycloheptylmethyl, cyclooctylmethyl; Het-alkyl such as (especially) 2- or 3-thienylmethyl, 1- or 2-(2-thienyl)-ethyl; Ar'-alkyl such as 4-biphenylyl-methyl, 2'-carboxy-4-biphenylylmethyl, 2'-methoxycarbonyl-4-biphenylylmethyl, 2'-ethoxycarbonyl-4-biphenylylmethyl, 2'-cyano-4-biphenylylmethyl, 2'-(1H-5-tetrazolyl)-4-biphenylylmethyl; R^6-CO-alkyl such as 2-oxopropyl, 2-oxobutyl, 3-methyl-2-oxobutyl, 3,3-dimethyl-2-oxobutyl; Ar-CO-alkyl such as benzoyl-methyl, o-, m- or p-carboxybenzoylmethyl, o-, m- or p-methoxycarbonylbenzoylmethyl, o-, m- or

p-ethoxy-carbonylbenzoylmethyl, o-, m- or p-cyanobenzoylmethyl, o-, m- or p-nitrobenzoylmethyl, o-, m- or p-aminobenzoylmethyl; Het-CO-alkyl such as 2-thienylcarbonyl-methyl. If an H atom in the "alkyl" moiety of the radical R^3 is replaced by COOH or COOA, the said radical is preferably, for example, α-ethoxycarbonylbenzyl, α-cyclo-hexyl-α-ethoxycarbonylmethyl, 1-ethoxycarbonyl-2-phenyl-ethyl.

The radical R^4 is preferably H.

The radicals R^5 and R^6 are each preferably A such as methyl or ethyl, and trifluoromethyl, furthermore preferably fluoromethyl, difluoromethyl, pentafluoroethyl or heptafluoropropyl.

The compounds of formula I can possess one or more chiral centres and can therefore exist in different forms (optically active or optically inactive). Formula I includes all these forms.

Accordingly, the invention relates especially to those compounds of formula I in which at least one of said radicals has one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following partial formulae Ia to Id which correspond to the formula I and wherein the radicals not described more precisely have the meanings stated for formula I but wherein:

in Ia	R^1	is alkyl having 1-6 C atoms;
in Ib	R^2	is COOH, $COOCH_3$, $COOC_2H_5$, CN, $CONH_2$, NO_2 or 1H-5-tetrazolyl;
in Ic	R^2	COOH, $COOCH_3$, $COOC_2H_5$, CN, $CONH_2$, NO_2 or 1H-5-tetrazolyl and is in the p position;
in Id	R^2	is alkyl having 1-6 C atoms and
	R^2	is COOH, $COOCH_3$, $COOC_2H_5$, CN, $CONH_2$, NO_2 or 1H-5-tetrazolyl.

Compounds which are furthermore preferred are those of the formulae:
Ie and Iae, Ibe, Ice and Ide, which correspond to the formulae I and Ia, Ib, Ic and Id but wherein additionally R^3 is H;

If and Iaf, Ibf, Icf and Idf, which correspond to the formulae I and Ia, Ib, Ic and Id but wherein additionally R^3 is Ar-alkyl;

Ig and Iag, Ibg, Icg and Idg which correspond to the formulae I and Ia, Ib, Ic and Id but wherein additionally R^3 is benzyl, carboxybenzyl, methoxycarbonylbenzyl, cyanobenzyl, nitrobenzyl or aminobenzyl;

Ih and Iah, Ibh, Ich and Idh which correspond to the formulae I and Ia, Ib, Ic and Id, but wherein additionally

R^3 is cycloalkylalkyl having 3-8 C atoms in the cycloakyl group;

Ii and Iai, Ibi, Ici and Idi which correspond to the formulae I and Ia, Ib, Ic and Id but wherein additionally R^3 is Het-alkyl;

Ij and Iaj, Ibj, Icj and Idj which correspond to the formulae I and Ia, Ib, Ic and Id but wherein additionally R^3 is Ar'-alkyl;

Ik and Iak, Ibk, Ick and Idk which correspond to the formulae I and Ia, Ib, Ic and Id but wherein additionally R^3 is R^6-CO-alkyl;

Il and Ial, Ibl, Icl and Idl which correspond to the formulae I and Ia, Ib, Ic and Id but wherein additionally R^3 is Ar-CO-alkyl;

Im and Iam, Ibm, Icm and Idm which correspond to the formulae I and Ia, Ib, Ic and Id but wherein additionally R^3 is Het-CO-alkyl;

In and Ian, Ibn, Icn and Idn which correspond to the formulae I and Ia, Ib, Ic and Id, but wherein additionally

R^3 is H, benzyl, carboxybenzyl, methoxycarbonylbenzyl, cyanobenzyl, nitrobenzyl, aminobenzyl, α-carboxy-α-cyclohexylmethyl, α-cyclohexyl-α-methoxycarbonylmethyl, thienylmethyl, carboxy-4-biphenylylmethyl, methoxy-carbonyl-4-biphenylylmethyl, (1H-5-tetrazolyl)-4-biphenylylmethyl or 3,3-dimethyl-2-oxobutyl;

Io and Iao, Ibo, Ico and Ido which correspond to the formulae I and Ia, Ib, Ic and Id but wherein additionally

R^3 is H, benzyl, p-carboxybenzyl, α-carboxybenzyl, p-methoxycarbonylbenzyl, α-methoxycarbonylbenzyl, p-cyanobenzyl, p-nitrobenzyl, p-aminobenzyl, α-carboxy-α-cyclohexylmethyl, α-cyclohexyl-α-methoxycarbonymethyl, 2-thienylmethyl, 2'-carboxy-4-biphenylylmethyl, 2'-methoxycarbonyl-4-biphenylylmethyl, 2'-(1H-5-tetrazolyl)-4-biphenylylmethyl or 3,3-dimethyl-2-oxo-butyl.

Particularly preferred compounds are all those of the abovementioned formulae in which additionally Y is O and/or R^4 is H.

The compounds of formula I and also the starting materials for their preparation are moreover prepared by methods known per se, such as those described in the literature (for example in the standard works like Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart, but especially in European Patent Application A2-0 430 709 and US Patent 4 880 804), under reaction conditions which are known and suitable for said reactions, it also being possible to make use of variants known per se, which are not mentioned in greater detail here.

If desired, the starting materials can also be formed in situ, so that they are not isolated from the reaction mixture but immediately reacted further to give the compounds of formula I.

The compounds of formula I can preferably be obtained by reacting compounds of formula II with compounds of formula III.

In the compounds of formula II, E is preferably Cl, Br, I or an OH group which has been functionally modified to acquire reactivity, such as alkylsulfonyloxy having 1-6 C atoms (preferably methylsulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (preferably phenyl- or p-tolyl-sulfonyloxy).

The reaction of II with III is conveniently carried out by first converting III to a salt by treatment with a base, for example with an alkali metal

alcoholate such as CH_3ONa or potassium tert-butylate in an alcohol such as CH_3OH or in an amide such as dimethylformamide (DMF), or with an alkali metal hydride such as NaH or an alkali metal alcoholate in DMF, and then reacting said salt with II in an inert solvent, for example an amide such as DMF or dimethylacetamide, or a sulfoxide such as dimethyl sulfoxide (DMSO), conveniently at temperatures of between -20 and 100°, preferably of between 10 and 30°. Other suitable bases are alkali metal carbonates such as Na_2CO_3 or K_2CO_3, or alkali metal hydrogen carbonates such as $NaHCO_3$ or $KHCO_3$.

Some of the starting materials, especially those of formula II, are known. If they are not known, they can be prepared by known methods in analogy to known substances. Compounds of the formula III (R^3 = H) can be obtained for example by condensation of 3,4-diamino-6-R^4-1,2-dihydro-2-oxo- (or -2-thioxo-)-pyridines or of 3,4-diamino-2-chloro-6-R^4-pyridines with carboxylic acids of the formula R^1-COOH in the presence of polyphosphoric acid.

A compound of formula I can also be liberated from one of its functional derivatives by treatment with a solvolysing (for example hydrolysing) or hydrogenolysing agent.

Thus it is possible, using one of the methods indicated, to prepare a compound which has formula I but in which a 5-tetrazolyl group is replaced with a 5-tetrazolyl group functionally modified in the 1- position (protected by a protecting group). Examples of suitable protecting groups are: triphenylmethyl, which can be eliminated with HCl or formic acid in an inert solvent or solvent mixture, for example methanol or ether/dichloromethane/methanol; 2-cyanoethyl, which can be eliminated with NaOH in water/THF; and p-nitro-benzyl, which can be eliminated with H_2/Raney nickel in ethanol (compare European Patent Application A2-0 291 969).

It is also possible to convert one compound of formula I to another compound of formula I by converting

one or more of the radicals R^1, R^2, R^3, R^4 and/or Y to other radicals R^1, R^2, R^3, R^4 and/or Y, for example by reducing nitro groups to amino groups (for example by hydrogenation on Raney nickel or Pd/charcoal in an inert solvent such as methanol or ethanol), and/or functionally modifying free amino and/or hydroxyl groups, and/or freeing functionally modified amino and/or hydroxyl groups by solvolysis or hydrogenolysis, and/or replacing halogen atoms with CN groups (for example by reaction with copper(I) cyanide), and/or hydrolysing nitrile groups to COOH groups or to $CONH_2$ groups, or converting nitrile groups to tetrazolyl groups with hydrazoic acid derivatives, for example sodium azide in N-methylpyrrolidone or trimethyltin azide in toluene.

Thus, for example, free amino groups can be acylated in conventional manner with an acid chloride or anhydride, or free hydroxyl and/or NH groups can be alkylated with an unsubstituted or substituted alkyl or Ar-alkyl halide or with aldehydes such as formaldehyde, in the presence of a reducing agent such as $NaBH_4$ or formic acid, conveniently in an inert solvent such as methylene chloride or THF, and/or in the presence of a base such as triethylamine or pyridine, at temperatures of between -60 and +30°.

If desired, a functionally modified amino and/ or hydroxyl group in a compound of formula I can be freed by solvolysis or hydrogenolysis using conventional methods. Thus, for example, a compound of formula I containing an $NHCOR^5$ or COOA group can be converted to the corresponding compound of formula I containing an NH_2 or COOH group instead. Ester groups can be hydrolysed for example with NaOH or KOH in water, water/THF or water/dioxane, at temperatures of between 0 and 100°.

The reaction of nitriles of formula I (R^2 = CN or R^3 = cyanoalkyl) with hydrazoic acid derivatives leads to tetrazoles of formula I (R^2 = 1H-5-tetrazolyl and/or R^3 = 1H-5-tetrazolylalkyl). It is preferable to use trialkyltin azides such as trimethyltin azide, in an

inert solvent, for example an aromatic hydrocarbon such as toluene, at temperatures of between 20 and 150°, preferably of between 80 and 140°, or sodium azide in N-methylpyrrolidone at temperatures of between about 100 and 200°.

A base of formula I can be converted with an acid to the corresponding acid addition salt. Possible acids for this reaction are especially those which yield physiologically acceptable salts. Thus it is possible to use inorganic acids, for example sulfuric acid, nitric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, and sulfamic acid, as well as organic acids, especially aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethane-sulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalene-monosulfonic and -disulfonic acids and lauryl sulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used for isolating and/or purifying the compounds of formula I.

On the other hand, compounds of formula I containing COOH or tetrazolyl groups can be converted with bases (for example sodium or potassium hydroxide or carbonate) to the corresponding metal salts, especially alkali metal or alkaline earth metal salts, or to the corresponding ammonium salts. The potassium salts are particularly preferred.

The novel compounds of formula I and their physiologically acceptable salts can be used for the preparation of pharmaceutical formulations by

incorporation into a suitable dosage form together with at least one excipient or adjunct and, if desired, together with one or more other active ingredients. The resulting formulations can be used as drugs in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (for example oral or rectal) or parenteral administration or for administration in the form of an inhalation spray, and which do not react with the novel compounds, examples being water, vegetable oils, benzyl alcohols, polyethylene glycols, glycerol triacetate and other fatty acid glycerides, gelatin, soya lecithin, carbohydrates such as lactose or starch, magnesium stearate, talc and cellulose. Tablets, coated tablets, capsules, syrups, juices or drops, in particular, are used for oral administration; lacquered tablets and capsules with coatings or shells resistant to gastric juices are of special interest. Suppositories are used for rectal administration, and solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions or implants, are used for parenteral administration. For administration as inhalation sprays, it is possible to use sprays containing the active ingredient either dissolved or suspended in a propellant or propellant mixture (for example hydrocarbons such as propane or butane, or fluorocarbons such as heptafluoropropane). It is convenient here to use the active ingredient in micronised form, it being possible for one or more additional physiologically compatible solvents, for example ethanol, to be present. Inhalation solutions can be administered with the aid of conventional inhalers. The novel compounds can also be lyophilised and the resulting lyophilisates used for example for the manufacture of injectable preparations. The indicated formulations can be sterilised and/or can contain adjuncts such as preservatives, stabilisers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances and colours and/or

flavourings. If desired, they can also contain one or more other active ingredients, for example one or more vitamins, diuretics or antiinflammatory agents.

The substances according to the invention are normally administered in analogy to other known, commercially available preparations, but in particular in analogy to the compounds described in US Patent 4 880 804, preferably in doses of between about 1 mg and 1 g, especially of between 50 and 500 mg per dosage unit. The daily dose is preferably between about 0.1 and 100 mg/kg, especially between 1 and 50 mg/kg of body weight. However, the particular dose for each individual patient depends on a very wide variety of factors, for example on the efficacy of the particular compound used, age, body weight, general state of health, sex, diet, time and mode of administration, rate of excretion, drug combination and severity of the particular disease to which the therapy is applied. Oral administration is preferred.

Hereinbefore and hereinafter, all temperatures are given in °C. In the following Examples, "conventional working-up" means: Water is added if necessary, the pH is adjusted to between 2 and 10 if necessary, depending on the constitution of the end product, extraction is carried out with ethyl acetate or methylene chloride, and the organic phase is separated off, dried over sodium sulfate, evaporated and purified by chromatography on silica gel and/or by crystallisation. Rf = Rf on silica gel (by thin layer chromatography; eluent: ethyl acetate/methanol 9:1). DOI = -4,5-dihydro-4-oxo-3H-imidazo[4,5-c]pyridine.

Example 1

19.1 g of 2-butyl-4,5-dihydro-4-oxo-1(or 3)H-imidazo[4,5-c]pyridine (m.p. 285-290°; obtainable by heating 3,4-diamino-2-chloropyridine and valeric acid in polyphosphoric acid at 100-140°, then 170-180°) are dissolved in 500 ml of DMF, 16.6 g of K_2CO_3 are added, the mixture is stirred for 45 min, a solution of 27.45 g of methyl p-bromomethylbenzoate is added dropwise, the mixture is stirred at 20° for 16 h, and water is added. The precipitate which has separated out is filtered off, washed with water, dried and chromatographed on silica gel. Using ethyl acetate and then ethyl acetate/methanol, first 2-butyl-3,5-bis-p-methoxycarbonylbenzyl-DOI (m.p. 124°) is obtained, and then 2-butyl-3-p-methoxycarbonylbenzyl-DOI (m.p. 219°).

Obtained analogously using p-bromomethylbenzonitrile are 2-butyl-3,5-bis-p-cyanobenzyl-DOI (m.p. 122.5°) and 2-butyl-3-p-cyanobenzyl-DOI (m.p. 201°).

Obtained analogously from 4,5-dihydro-4-oxo-2-propyl-1(or 3)H-imidazo[4,5-c]pyridine (m.p. 258°; obtainable from 3,4-diamino-2-chloropyridine and butyric acid in polyphosphoric acid) are 3,5-bis-p-methoxycarbonylbenzyl-2-propyl-DOI (oily; Rf 0.51 in ethyl acetate) and 3-p-methoxycarbonylbenzyl-2-propyl-DOI, m.p. 235°.

Example 2

Obtained in analogy to Example 1 from 2-butyl-5-(α-cyclohexyl-α-methoxycarbonylmethyl)-DOI (obtainable by benzylation of 2-butyl-4,5-dihydro-4-oxo-1(or 3)H-imidazo[4,5-c]pyridine to give the 3-benzyl-3H-compound, reaction with methyl α-bromo-α-cyclohexylacetate to give 2-butyl-3-benzyl-5-(α-cyclohexyl-α-methoxycarbonylmethyl)-DOI and elimination of the benzyl group by hydrogenolysis) and methyl p-bromomethylbenzoate is 2-butyl-5-(α-cyclohexyl-α-methoxycarbonylmethyl)-3-p-methoxycarbonylbenzyl-DOI, Rf 0.63.

Example 3

1.34 g of K tert.-butylate are added under N_2 to a solution of 3.39 g of 2-butyl-3-p-methoxycarbonyl-benzyl-DOI (m.p. 218-219°) in 85 ml of DMF, the mixture is stirred at 20° for 10 min, a solution of 2.16 g of p-nitrobenzyl bromide in 35 ml of DMF is added, and the mixture is stirred at 20° for 2.5 h. Conventional working-up (chromatography on silica gel, ethyl acetate) results in 2-butyl-3-p-methoxycarbonylbenzyl-5-p-nitro-benzyl-DOI, m.p. 142°.

Obtained analogously using 2-thienylmethyl chloride is 2-butyl-3-p-methoxycarbonylbenzyl-5-(2-thienylmethyl)-DOI.

Obtained analogously using methyl α-bromo-α-cyclohexylacetate is 2-butyl-5-(α-cyclohexyl-α-methoxy-carbonylmethyl)-3-p-methoxycarbonylbenzyl-DOI, Rf. 063.

Obtained analogously using methyl α-bromo-α-phenylacetate is 2-butyl-3-p-methoxycarbonylbenzyl-5-α-methoxycarbonylbenzyl-DOI, Rf 0.47 (ethyl acetate/hexane 9:1).

Obtained analogously using methyl 2-bromo-3-phenylpropionate is 2-butyl-3-p-methoxycarbonylbenzyl-5-(1-methoxycarbonyl-2-phenylethyl)-DOI, Rf 0.64.

Obtained analogously from 3-p-methoxycarbonyl-benzyl-2-propyl-DOI are the following 3-p-methoxycar-bonylbenzyl-2-propyl-DOI:
5-Benzyl-
5-p-Nitrobenzyl-
5-(3,3-Dimethyl-2-oxo-butyl)-.

Obtained analogously from 2-butyl-3-p-cyano-benzyl-DOI using methyl 4'-bromomethylbiphenyl-2-car-boxylate is 2-butyl-3-p-cyanobenzyl-5-(2'-methoxy-carbonylbiphenylyl-4-methyl)-DOI, m.p. 65°.

Obtained analogously from 2-butyl-3-p-cyano-benzyl-DOI using chloroacetonitrile is 2-butyl-3-p-cyanobenzyl-5-cyanomethyl-DOI, m.p. 197°.

Example 4

3 g of 2-butyl-4,5-dihydro-4-oxo-1(or 3)H-imidazo[4,5-c]pyridine are dissolved in 75 ml of methanol and, while stirring at 20°, a solution of 0.4 g of Na in 10 ml of methanol is added dropwise. The mixture is stirred for 45 min and then evaporated, the residue is dissolved in 30 ml of DMF and cooled to 0°, and, at this temperature, a solution of 3.7 g of p-nitrobenzyl bromide is added, and the mixture is stirred at 20° for 16 h. Evaporation and conventional working-up results, after chromatography (silica gel; ethyl acetate/toluene 7:3), first in 2-butyl-3,5-bis-p-nitrobenzyl-DOI (m.p. 142-143°) and then 2-butyl-3-p-nitrobenzyl-DOI (m.p. 193-194°).

Example 5

1 g of 2-butyl-3-p-methoxycarbonylbenzyl-5-p-nitrobenzyl-DOI is dissolved in 50 ml of methanol and hydrogenated on 0.5 g of Pd-c (5%) at 20° and under 1 bar until the H_2 uptake ceases, and the mixture is filtered and, after evaporation and chromatography on silica gel (ethyl acetate/methanol 9:1), results in 5-p-aminobenzyl-2-butyl-3-p-methoxycarbonylbenzyl-DOI, m.p. 59-60°.

Example 6

A mixture of 1 g of 2-butyl-3-p-methoxycarbonyl-benzyl-5-p-nitrobenzyl-DOI, 20 ml of 1 N sodium hydroxide solution, 6 ml of methanol and 18 ml of THF is stirred at 20° for 16 h and is acidified with hydrochloric acid, and conventional working-up results in 2-butyl-3-p-carboxy-benzyl-5-p-nitrobenzyl-DOI, m.p. 170°.

The following DOI are obtained analogously by hydrolysis of the corresponding methyl esters:

5-p-Aminobenzyl-2-butyl-3-p-carboxybenzyl-, m.p. 130°

2-Butyl-3-p-carboxybenzyl-, m.p. 249°

2-Butyl-3,5-bis-p-carboxybenzyl, m.p. 150°

3-p-Carboxybenzyl-2-propyl-, m.p. 289°

3,5-Bis-p-carboxybenzyl-2-propyl-, m.,p. 209°

5-Benzyl-3-p-carboxybenzyl-2-butyl-, m.p. 212°, K salt, m.p. > 300°

3-p-Carboxybenzyl-5-p-nitrobenzyl-2-propyl-, m.p. 300°
2-Butyl-3-p-carboxybenzyl-5-(2-thienylmethyl)-, m.p. 201°
3-p-Carboxybenzyl-5-(3,3-dimethyl-2-oxo-butyl)-2-propyl-, m.p. 195°
2-Butyl-3-p-carboxybenzyl-5-α-carboxy-α-cyclohexyl-methyl-, m.p. 195°
2-Butyl-3-p-carboxybenzyl-5-α-carboxybenzyl-, sesquihydrate, m.p. 234°
2-Butyl-3-p-carboxybenzyl-5-(1-carboxy-2-phenyl-ethyl)-, m.p. 253°.

Example 7

Reaction of 2-butyl-3-p-cyanobenzyl-5-(2'-methoxycarbonylbiphenyl-4-methyl)-DOI in analogy to Example 6 with sodium hydroxide solution/methanol/THF results in 2-butyl-3-p-carbamoylbenzyl-5-(2'-carboxy-biphenylyl-4-methyl)-DOI, m.p. 241°, as main product.

Example 8

a) A mixture of 4.21 g of 2-butyl-3,5-bis-p-cyano-benzyl-DOI, 41.2 g of trimethyltin azide and 300 ml of toluene is boiled for 72 h and evaporated. The residue is stirred with 100 ml of methanolic hydrochloric acid at 20° for 2 h, and conventional working-up (saturated NaCl solution/dichloromethane) results in 2-butyl-3,5-bis-[p-(1H-5-tetrazolyl)-benzyl]-DOI, m.p. 272°.

Obtained analogously from 2-butyl-3-p-cyanobenzyl-DOI is 2-butyl-3-[p-(1H-5-tetrazolyl)benzyl]-DOI.

Obtained analogously from 2-butyl-3-p-cyanobenzyl-5-(2'-methoxycarbonylbiphenylyl-4-methyl)-DOI is 2-butyl-5-(2'-methoxycarbonylbiphenylyl-4-methyl)-3-[p-(1H-5-tetrazolyl)benzyl]-DOI, m.p. 154°.

Obtained analogously from 2-butyl-3-p-cyanobenzyl-5-cyanomethyl-DOI is 2-butyl-3-[p-(1H-5-tetrazolyl)-benzyl]-5-(1H-5-tetrazolylmethyl)-DOI, m.p. 276° (decomposition).

The following Examples relate to pharmaceutical formulations containing active ingredients of formula I or their salts.

Example A: Tablets and coated tablets

Tablets of the following composition are produced by compression in conventional manner and, where required, are provided with a conventional sucrose-based coating:

Active ingredient of formula I	100 mg
Microcrystalline cellulose	278.8 mg
Lactose	110 mg
Maize starch	11 mg
Magnesium stearate	5 mg
Finely divided silicon dioxide	0.2 mg

Example B: Hard gelatin capsules

Conventional two-piece hard gelatin capsules are each filled with

Active ingredient of formula I	100 mg
Lactose	150 mg
Cellulose	50 mg
Magnesium stearate	6 mg

Example C: Soft gelatin capsules

Conventional soft gelatin capsules are filled with a mixture of 50 mg of active ingredient and 250 mg of olive oil in each case.

Example D: Ampoules

A solution of 200 g of active ingredient in 2 kg of 1,2-propanediol is made up to 10 l with water and filled into ampoules so that each ampoule contains 20 mg of active ingredient.

Example E: Aqueous suspension for oral administration

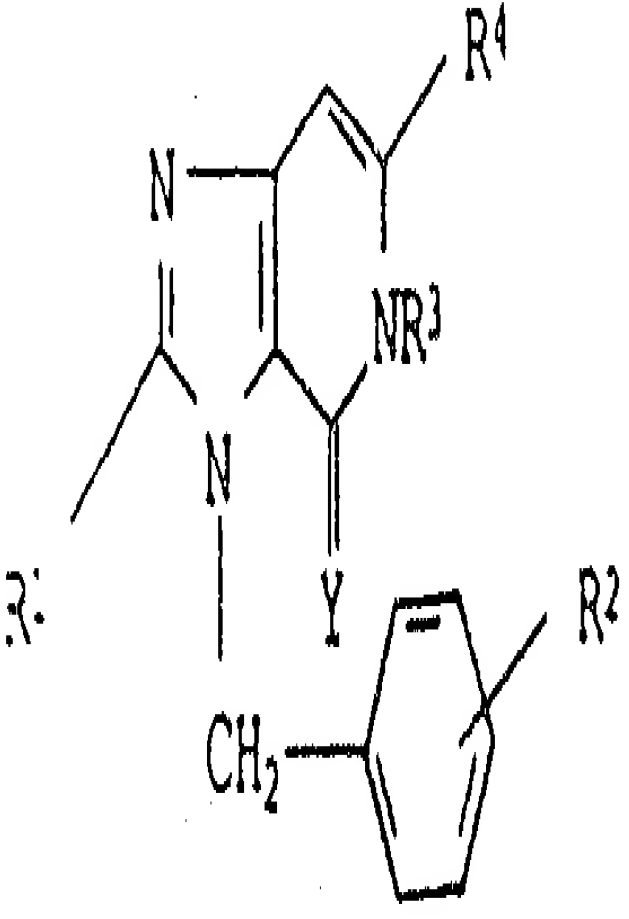
An aqueous suspension is prepared in conventional manner. The unit dose (5 ml) contains 100 mg of active ingredient, 100 mg of sodium carboxymethylcellulose, 5 mg of sodium benzoate and 100 mg of sorbitol.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente


R1
N
NR3
N
Y
R2
CH2